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International Preliminary Examining Authority
European Patent Office
PB 5818 Patentlaan 2
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YOUR REF

OUR REF
P029491WO: CPM/PMJ

13th January 2004

Dear Sirs,

Re: International Patent Application No. PCT/GB03/000301
Heightman, Nicholas John et al.

In response to the first Written Opinion of 17th October 2003, I enclose a fresh set of claims in triplicate. I request that this be substituted for the set currently on file. Replacement amended pages 1 and 2 that reflect the amendments to claim 1 are also enclosed in triplicate. Copies of the original pages showing the amendments that have been made are also enclosed for reference.

The Applicants ask for the following comments to be taken into account when the International Preliminary Examination Report is prepared.

Amendment

The term *"filler layer"* of claim 1 should be amended to read *"cream filling layer"*. Support for this is to be found on original page 2 at lines 24 and 25 of the specification which states *"The "sandwich biscuit" of the present invention may comprise a cream or other filling layer..."*. The description on page 2 has now been amended to refer only to the cream filling layer.

The term *"medicated substance"* in claim 1 has also been amended to read *"medicinal substance as used in compliance with a drug treatment dosage regime"*. Support for this amendment is to be found in the specification on page 1, lines 27 to 29. The final two lines of claim 1 also imply this.

Finally, the list of suitable medicinal substances in claim 5 has been amended for consistency with the foregoing amendments.

FACSIMILE MESSAGE

To: **EPO Hague**
Fax No.: **00 31 70 340 3016**

This fax consists of 19 sheets. If a sheet is missing or has been imperfectly received, please contact us immediately (Tel: 020-7242 8692; Fax: 020-7405 4166). If you are not the addressee, please contact us immediately and then destroy this fax.

Novelty

Citation D1 (EP 0306469)

Citation D1 discloses filling compositions comprising (1) psyllium fibre, (2) glycerin and, optionally, (3) at least one sweetener; and (4) at least one flavourant in specified quantities (see page 1, lines 54 to 56). The filling compositions of the present invention may be used as a filling for a sandwich-type biscuit/cookie (see page 2, lines 19 to 20, and page 6, lines 37 to 40). Additional optional components of the filling include pharmaceutical actives such as stimulants, antispasmodics, topical anaesthetics, and anti-inflammatories (see page 4, lines 40 and 41). However, the fillings referred to in citation D1 are fruit fillings and not cream fillings (see page 1, line 30 and page 6, line 37 and other examples).

There is no disclosure of cream fillings in citation D1 and therefore the claims have novelty over this citation.

Citation D2 (GB 993308)

Citation D2 discloses a dietary product which may consist of two biscuits with filling between them, or it may take the form of a multi-layer sandwich, in which two or more layers of filling are separated by and contained between biscuits (see page 1, lines 47 to 51). Claim 1 of citation D2 states that the filling comprises a carbohydrate and a finely divided bulking agent dispersed throughout a fatty matrix, the bulking agent being substantially insoluble in the fat. Sodium carboxymethyl cellulose and guar gum are specified as bulking agents in claims 12 and 14 of citation D2. However amended claim 1 of the present application makes it clear that *"medical substances"* are substances used a part of a dosage regime. Such substances are completely different from bulking agents for use in dietary regimes, such as carboxymethyl cellulose. Bulking agents do not fall within the scope of amended claim 1.

As amended, the claims of the present application are thus novel over citation D2.

Citation D3 (US 593127)

D3 discloses fat-reduced sandwich biscuits/cookies that "*possess similar organoleptic properties to traditional full fat cookie cream-filled counterparts*", (see column 1, lines 22, 23, 28 and 29). The special formulation claimed in D3 is said to allow the preparation of a cream filling that incorporates inulin. Citation D3 defines inulin as being a non-crystalline, fibrous solid polysaccharide or mixture of polysaccharides containing beta-1,2 bonded glucofructan polymers of varying molecular weights terminated at the reducing end by a glucose ring. It is thus clear that inulin is not a "medical substance" as claimed in the present invention. There is no disclosure in citation D3 of the addition of any further medicinal substance to the cream filling.

The present invention as now claimed therefore has novelty over citation D3.

Citation D4 (EP 0347014) / NOT ARGUED

The Written Opinion mentions citation D4, but does not discuss its content. D4 relates to edible baked compositions comprising cholestyramine, preferably in the form of a nutrition bar or cookie. The Applicants can find no disclosure of a sandwich biscuit or cream filling of claim 1 of the present application in citation D4 and therefore do not believe that it is relevant to the present invention.

Inventive Step

The present invention is directed to the problem of administering a medicinal substance that is required in large amounts and is of unpalatable material, in a product that is both palatable and familiar to the patient. The medicinal substance may, for example, have a gritty texture or a chalky texture or other unpleasant mouth feel. This is explained in the specification from page 1, line 27 to page 2, line 5. The present invention solves this problem by adopting a sandwich biscuit as the vehicle for administration and also adopting a cream filling that disguises the unpalatable nature of the medicinal substance, particularly when present in large quantities. The present invention helps to ensure acceptability of the medicinal substance to the patient, and thereby improves patient compliance.

The Examiner states:

> *"It seems to be a straightforward possibility to employ the invention of D1 for taste masking of known bad-tasting drugs. The person skilled in art could hereby reasonably expect success in applying the solution of taste masking of the prior art to the known problem, that is an otherwise unpalatable medicament."*

The Applicants strongly disagree and do not believe that there is anything in the cited prior art that would have led the skilled reader to adopt the particular formulation claimed in the present invention. Citation D1 teaches a quite different approach to the problem of producing high fibre edible products containing psyllium. The unacceptable flavour of psyllium in citation D1 is disguised by adding sugar and/or flavour (see page 2, line 28 of citation D1) and adding fruit filling (see page 2, line 30 of citation D1). In fact, very large quantities of sweetener are added to the fillers of citation D1 in order to mask unpleasant flavours. Both Example I and Example III describe fillings in which the major component is the combination of sorbitol, dextrose and crystalline fructose. The skilled reader of citation D1 is therefore taught to adopt sweeteners and fruit achieve a masking effect and would not have been led to adopt the different approach of the present invention in using a cream filling for taste masking. Citation D1 thus does not have any teaching that would have suggested the adoption of a cream filling to the skilled reader. The Applicants therefore believe that, contrary to the Examiner's assertion, the claims of the present application have an inventive step over this citation.

The Applicants therefore believe that claim 1 as amended has both novelty and an inventive step over all of the cited prior art and accordingly request a favourable opinion in the International Preliminary Examination Report.

The Applicants note the Examiner's request that a description of the cited prior art should be inserted in the specification, but wish to defer this until a later stage.

Yours truly,

MERCER, Christopher Paul

FORMULATION FOR THE ADMINISTRATION OF MEDICINAL SUBSTANCES

FIELD OF INVENTION

This invention relates to a new formulation for the administration of medicinal substances within traditional baked food products, in particular within sandwich biscuits.

BACKGROUND OF THE INVENTION

Many medicines are potent materials requiring small amounts for their effectiveness, but there are other medicines that must be administered in large doses. Conventional formulations such as tablets and capsules can accommodate up to 1000mg of active ingredient but the products are very large and many patients find them difficult to swallow. In many cases the physical properties of the medicinal substance preclude dosages in excess of 250-500mg as they require dilution in inert materials to render them suitable for processing. Dosages of the order of several or many grammes per day require the patient to take many tablets. Some medicines such as cholestyramine resin are presented in sachets for dispersion in water. The products are not very palatable and are inelegant, again resulting in problems with patient acceptability and compliance.

It is known that medicines can be made more palatable or their presence disguised by incorporating the medicines within pre-cooked biscuits that have been reduced to crumb form. However, this requires intervention on behalf of the person making up the mixture and relies on their skill in ensuring that both a full dose of medicine is incorporated within the mixture and that the patient consumes all of the mixture. It is also known that certain therapeutic substances can be incorporated within biscuits during the initial cooking step, but this is not always satisfactory, particularly if the incorporated substance is adversely affected by the cooking process. There thus remains a need to provide alternative formulations for unpalatable medicinal, i.e. pharmaceutically active, substances.

It is the purpose of the present invention to allow the inclusion of active medicinal substances in readily acceptable formulations in such a way that compliance with drug treatment dosage regimes in enhanced. The present invention also addresses the problem of allowing large dosages of drugs to be administered effectively, especially as it has often not previously been convenient to administer such dosages by known administration routes. Many treatment regimes achieve sub-optimal therapeutic results because patients for whom the treatment is prescribed find that it is unpleasant to take the drug in the

inadequate quantities. The present invention permits the administration of large amounts of unpalatable material - for example with a gritty texture or a chalky texture or other unpleasant mouth feel, in a product which both palatable and familiar to the patient. This helps to ensure acceptability to the patient, and thereby improve patient compliance.

We have found that the formulation according to the present invention can be adapted to carry relatively high quantities of medicinal drug substances and combination of medicinal substances in such a way that chewing in the mouth facilitates swallowing. without adversely affecting the taste or mouthfeel of the biscuit. This makes the administration of drugs much more acceptable to many patients who find it difficult to swallow conventional pills and capsules. A further advantage is that formulations of the present invention have a texture that masks unpleasant mouth feel, such as gritty texture or chalkiness of some medicinal substances. The new formulations are also particularly suitable for the long-term administration of medicinal substances.

SUMMARY OF THE INVENTION

According to the present invention there further provided a formulation for the administration of a medical substance as used in compliance with a drug treatment dosage regime comprising a sandwich biscuit having two or more biscuit layers that support cream filling layer(s), in which the cream filling layer, and optionally the biscuit layers, comprise(s) a dosage unit form, or a multiple or sub-multiple thereof, of an unpalatable medicament. A further aspect of the invention is that the cream filling layer can contain a large amount of medicinal substance without having a deleterious effect on the mouth feel or palatability of the product.

The "sandwich biscuit" of the present invention may comprise a cream filling layer supported between any convenient number of dry layers, normally two layers, of biscuit. The biscuit layer of the sandwich biscuit may be a plain, non-medicated, biscuit layer or may itself contain a medicament. In the latter instance, it is possible to select a different medicament for the cream filler layer from that in the biscuit layer, whereby the two medicaments have a co-operating or synergistic effect. As already indicated, a medicine is unpalatable if it cannot be readily orally administered in its simple state, for example because of unpleasant mouth feel.

As indicated previously, the invention is of special value where relatively large amounts of active medicinal ingredient need be taken for the treatment to be effective, for

CLAIMS

1. A formulation for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime comprising a sandwich biscuit comprising two or more biscuit layers that support layers wherein the cream filling layer comprises a dosage unit form or multiple or sub-multiple thereof of an unpalatable medicament.

2. A formulation according to claim 1, in which the medicament has a gritty texture or a chalky texture or other unpleasant mouth feel.

3. A formulation according to claim 1 or 2, in which the medicament is present in an amount of greater than 500 mg per biscuit.

4. A formulation according to claim 3, in which the medicament is present in an amount of between 1g and 3g per biscuit

5. A formulation according to any of the foregoing claims, in which the medicinal substance is selected from the ion exchange resin substance VML252, optionally in combination of calcium carbonate, the ion exchange resin cholestyramine, optionally in combination chlofibrate, gemfibrozil and other orally active cholesterol-lowering materials, anthelmintic agents, metformin or gamma guanidinobutyramide and its pharmaceutically acceptable salts, optionally in combination of other oral agents used to treat diabetes type 2, optionally in combination with other agents for the oral treatment of obesity, and ion exchange resin suitable for treating elevated serum potassium, optionally in combination of with other oral agents used for treating elevated serum potassium.

6. A formulation according to claim 5, in which the anthelmintic agent is albendazole, febendazole, Ivermectin, thiabendazole and another bendazole substances

7. A formulation according to any of the foregoing claims comprising a biscuit layers comprise a medical substance, in which the medicinal substance in the biscuit and the

medicament in the cream filling layer have a co-operating or synergistic effect on administration.

8. A formulation according to any of claims 1 to 6, in which the biscuit layer is an oatmeal biscuit and the medicament is a cholesterol lowering pharmaceutical.

9. A formulation according to claim 1, substantially as hereinbefore described in any one of the Examples.

DUE 17.1.04

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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CARPMAELS & RANSFORD
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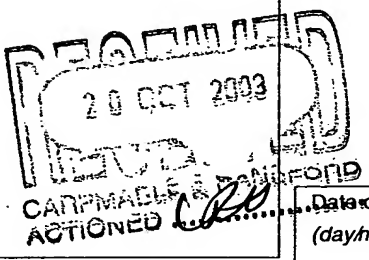
London WC1A 2RA
GRANDE BRETAGNE



PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	17.10.2003
Applicant's or agent's file reference: P029491WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB03/00301	23.01.2003	24.01.2002

International Patent Classification (IPC) or both national classification and IPC
A61K9/00

Applicant
HEIGHTMAN, Nicholas John et al

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24.05.2004

Name and mailing address of the international preliminary examining authority:

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WRITTEN OPINION

International application No. PCT/GB03/00301

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this opinion.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

WRITTEN OPINION International application No. PCT/GB03/00301

1. Statement

Novelty (N)	Claims	1-5,7-9
Inventive step (IS)	Claims	1-9
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: EP 0 306 469
D2: GB 993 308
D3: US 5 939 127
D4: EP 0 347 014

2 **NOVELTY** (Art. 33(2) PCT)

2.1 D1 discloses cookies having a filling comprising psyllium with increased palatability for control of blood cholesterol levels in the relevant amounts. Other agents may be added (D1, page 4, lines 36-42; page 4, lines 47-50; examples 1-3). Also the biscuit layers comprise a medical substance, in that in Example 2 sodium bicarbonate is used. Also other ingredients of the dough can be interpreted in broad terms as medical substance, due the absence of a clear meaning of the term "medical substance". The result to be achieved of claim 7 can not confer novelty as the claim does not have a technical feature disclosing how this effect can be achieved.

2.2 D2 discloses sandwich biscuits having a filling comprising a bulking agent such as carboxymethyl cellulose (D2, page 1, right column, lines 47-60 and lines 82-86; examples 1 and 2).

2.3 D3 discloses cookies filled with a cream, said cream comprising inulin (D3, column 2, lines 37-47; column 5, lines 45-53; example 1).

2.4 In view of D1-D3, the present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 1-5,7-9 is not new.

2.5 In view of the prior cited, claim 6 appears to be novel and meets therefore the

requirements of Art. 33(2) PCT.

3 INVENTIVE STEP (Art. 33(3) PCT)

3.1 Claims 1-5,7-9 do not involve an inventive step, because they are not new.

3.2 Even if the applicant could restore novelty of independent claim 1, an objection on ground of lack of an inventive step is likely to arise. Indeed, having regard to the claimed composition and the prior art, the person skilled in the art would regard the composition of the present invention (as far as novel) as an obvious alternative to those known.

3.3 Dependent claim 6 does not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step for the following reasons:

3.3.1 It seems to be a straightforward possibility to employ the invention of D1 for taste masking of known bad-tasting drugs. The person skilled in art could hereby reasonably expect success in applying the solution of taste masking of the prior art to the known problem, that is an otherwise unpalatable medicament.

3.4 Novelty provided, in view of the above, the present application seems not meet the requirements of Article 33(3) PCT, because the claimed subject-matter does not involve an inventive step.

4 Certain defects

4.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1-D3 is not mentioned in the description, nor are these documents identified therein. Furthermore, the documents upon which the description of the background art on page 1, lines 18-26, is based, are not disclosed.

4.2 If amendments are filed, it should be by way of replacement pages in the manner

stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

4.3 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

CLAIMS

1. A formulation for the administration of a medicinal substance as used in compliance with a drug treatment dosage regime comprising a sandwich biscuit comprising two ~~one~~ or more biscuit layers that support layers wherein the cream filling ~~filler~~ layer comprises a dosage unit form or multiple or sub-multiple ~~layer~~ thereof of an unpalatable medicament.

2. A formulation according to claim 1, in which the medicament has a gritty texture or a chalky texture or other unpleasant mouth feel.

3. A formulation according to claim 1 or 2, in which the medicament is present in an amount of greater than 500 mg per biscuit.

4. A formulation according to claim 3, in which the medicament is present in an amount of between 1g and 3g per biscuit

5. A formulation according to any of the foregoing claims, in which the medicinal substance is selected from the ion exchange resin substance VML252, optionally in combination of calcium carbonate, the ion exchange resin cholestyramine, optionally in combination chlofibrate, gemfibrozil and other orally active cholesterol-lowering materials, anthelmintic agents, metformin or gamma guanidinobutyramide and its pharmaceutically acceptable salts, optionally in combination of other oral agents used to treat diabetes type 2, carboxyl-methyl-cellulose and carboxyl-ethyl-cellulose, optionally in combination with other agents for the oral treatment of obesity, and ion exchange resin suitable for treating elevated serum potassium, optionally in combination of with other oral agents used for treating elevated serum potassium.

6. A formulation according to claim 5, in which the anthelmintic agent is albendazole, febendazole, Ivermectin, thiabendazole and another bendazole substances

7. A formulation according to any of the foregoing claims comprising a biscuit layers comprise a medical substance, in which the medicinal substance in the biscuit and the

FOR INFORMATION ONLY.

medicament in the cream filling ~~filler~~ layer have a co-operating or synergistic effect on administration.

8. A formulation according to any of claims 1 to 6, in which the biscuit layer is an oatmeal biscuit and the medicament is a cholesterol lowering pharmaceutical.

9. A formulation according to claim 1, substantially as hereinbefore described in any one of the Examples.